Exhibit 1

Goodman and Gilman's The Pharmacological Basis of Therapeutics

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lar to that of vinblastine, but there are some notable differences. An important feature is the incomplete cross-resistance between these agents, a remarkable finding in view of the very close similarity of their chemical structures and their common mechanism of action. Vincristine is effective in Hodgkin's disease and other lymphomas. Although it appears to be somewhat less beneficial than vinblastine when used alone in Hodgkin's disease, when used with mechlorethamine, prednisone, and procarbazine (the so-called MOPP regimen), it is the preferred treatment for the advanced stages (III and IV) of this disease (DeVita, 1981). In non-Hodgkin's lymphomas, vincristine is an important agent, particularly when used with cyclophosphamide, bleomycin, doxorubicin, and prednisone. As mentioned previously, vincristine is more useful than vinblastine in lymphocytic leukemia. Beneficial responses have been reported in patients with a variety of other neoplasms, particularly Wilms' tumor, neuroblastoma, brain tumors, rhabdomyosarcoma, and carcinomas of the breast, bladder, and the male and female reproductive systems (Calabresi *et al.*, 1985).

The clinical toxicity of vincristine is mostly neurological, as described above. The more severe neurological manifestations may be avoided or reversed by either suspending therapy or reducing the dosage upon occurrence of motor dysfunction. Severe constipation, sometimes resulting in colicky abdominal pain and obstruction, may be prevented by a prophylactic program of laxatives and hydrophilic agents.

Alopecia occurs in about 20% of patients given vincristine; however, it is always reversible, frequently without cessation of therapy. Although less common than with vinblastine, leukopenia may occur with vincristine, and thrombocytopenia, anemia, polyuria, dysuria, fever, and gastrointestinal symptoms have been reported occasionally. Ischemic cardiac toxicity has been reported. The syndrome of hyponatremia associated with high urinary concentration of Na^+ and inappropriate secretion of antidiuretic hormone has been occasionally observed during vincristine therapy. In view of the rapid action of the vinca alkaloids, it is advisable to take appropriate precautions to prevent the complication of hyperuricemia. This can be accomplished by the administration of allopurinol (*see* above).

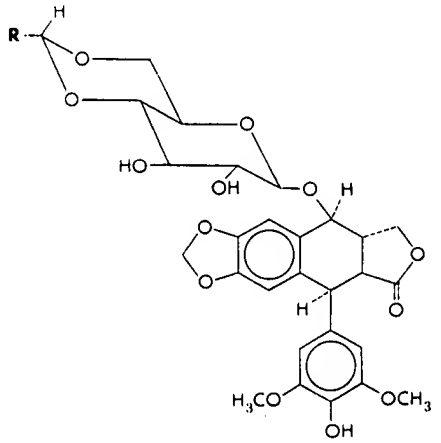
TAXOL

Taxol is an experimental antimitotic agent, isolated from the bark of the ash tree, *Taxus brevifolia*. It binds to tubulin (at a site distinct from that used by the vinca alkaloids) and promotes the assembly of microtubules (Schiff *et al.*, 1979). Cells resistant to vinca alkaloids because of mutations in tubulin remain sensitive to taxol, but multidrug-resistant cells that overexpress the P-glycoprotein are resistant to the drug (Racker *et al.*, 1986). Taxol is currently being evaluated clinically; it has activity against malignant melanoma and carcinoma of the ovary. Maximal doses are 30 mg/m^2 per day for 5 days or 210 to 250 mg/m^2 given once every 3 weeks. The primary toxicity of taxol is myelosuppression and a sensory neuropathy (Wiernik *et al.*, 1987).

EPIPODOPHYLLOTOXINS

Podophyllotoxin, extracted from the mandrake plant (or May apple), *Podophyllum peltatum*, was used as a folk remedy by the American Indians and early colonists for its emetic, cathartic, and anthelmintic effects. Two semisynthetic glycosides of the active principle, podophyllotoxin, have been developed that show significant therapeutic activity in several human neoplasms, including small-cell carcinomas of the lung, testicular tumors, Hodgkin's disease, and diffuse histiocytic lymphoma. These derivatives are referred to as etoposide (VP-16-213) and teniposide (VM-26). Although podophyllotoxin binds to tubulin at a site distinct from that for interaction with the vinca alkaloids, etoposide and teniposide have no effect on microtubular structure or function at usual concentrations. (For reviews of the epipodophyllotoxins, *see* Doyle, 1984; O'Dwyer *et al.*, 1985.)

Chemistry. The chemical structures of etoposide and teniposide are shown below:



Etoposide: **R** = CH_3

Teniposide: **R** =

They have been selected from many derivatives of podophyllotoxin that have been synthesized during the past 20 years.